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(PCT Rule 61.2)

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Date of mailing: 14 December 2000 (14.12.00)	
International application No.: PCT/EP00/04747	Applicant's or agent's file reference: JAB 1488-PCT
International filing date: 23 May 2000 (23.05.00)	Priority date: 02 June 1999 (02.06.99)
Applicant: DE BRUYN, Marcel, Frans, Leopold et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International preliminary Examining Authority on:
23 October 2000 (23.10.00)

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The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer: J. Zahra Telephone No.: (41-22) 338.83.38
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(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
14 December 2000 (14.12.2000)

PCT

(10) International Publication Number
WO 00/75137 A1(51) International Patent Classification⁷: C07D 405/14,
405/12, A61K 31/505, A61P 9/00

(21) International Application Number: PCT/EP00/04747

(22) International Filing Date: 23 May 2000 (23.05.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
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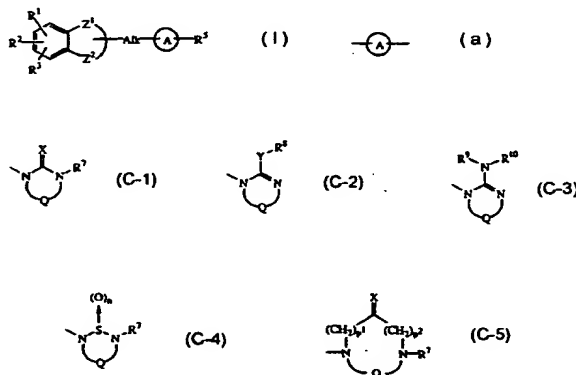
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AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE,
DK, DM, DZ, EE, ES, FI, GB, GD, GE, ~~GH~~, GM, HR, HU,
ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO,
NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR,
TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— With international search report.

[Continued on next page]

(54) Title: PYRROLIDINYL, PIPERIDINYL OR HOMOPIPERIDINYL SUBSTITUTED (BENZODIOXAN, BENZOFURAN
OR BENZOPYRAN) DERIVATIVES

(57) Abstract: The present invention concerns compounds of formula (I), a stereochemically isomeric form thereof, an *N*-oxide form thereof or a pharmaceutically acceptable acid addition salt thereof, wherein $-Z^1-Z^2-$ is a bivalent radical; R^1 , R^2 and R^3 are each independently selected from hydrogen, C_{1-6} alkyl, hydroxy, halo and the like; or when R^1 and R^2 are on adjacent carbon atoms, R^1 and R^2 taken together may form a bivalent radical of formula; Alk is optionally substituted C_{1-6} alkanediyl; the bivalent radical (a) is a substituted piperidinyl, an optionally substituted pyrrolidinyl, homopiperidinyl, piperazinyl or tropanyl; R^5 is a radical of formula (c-1), (c-2), (c-3), (c-4), (c-5) wherein n is 1 or 2; p^1 is 0, and p^2 is 1 or 2; or p^1 is 1 or 2, and p^2 is 0; X is oxygen, sulfur or $=NR^9$; Y is oxygen or sulfur; R^7 is hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl or phenylmethyl; R^8 is C_{1-6} alkyl, C_{3-6} cycloalkyl phenyl or phenylmethyl; R^9 is cyano, C_{1-6} alkyl, C_{3-6} cyclo-alkyl, C_{1-6} alkyloxycarbonyl or aminocarbonyl; R^{10} is hydrogen or C_{1-6} alkyl; and Q is a bivalent radical. Processes for preparing said products, formulations comprising said products and their use as a medicine are disclosed, in particular for treating conditions which are related to impaired fundic relaxation.

WO 00/75137 A1



For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

PYRROLIDINYL, PIPERIDINYL OR HOMOPIPERIDINYL SUBSTITUTED
(BENZODIOXAN, BENZOFURAN OR BENZOPYRAN) DERIVATIVES

- 5 The present invention is concerned with novel aminomethylchromane compounds having fundic relaxation properties. The invention further relates to methods for preparing such compounds, pharmaceutical compositions comprising said compounds as well as the use as a medicine of said compounds.
- 10 Structurally related aminomethylchromane derivatives are disclosed in US-5,541,199 as selective autoreceptor agonists useful as antipsychotic agents. Other structurally related aminomethylchroman derivatives having affinity for cerebral 5-hydroxytryptamine receptors of the 5-HT₁ type and therefore suitable for the treatment of disorders of the central nervous system are disclosed in US-5,137,901.
- 15 EP-0,546,388, published on 16 June 1993, discloses structurally related aminomethylchroman derivatives having affinity for cerebral 5-hydroxytryptamine receptors of the 5-HT₁ type and for dopamine receptors of the D₂-type. EP-0,628,310, published on 14 December 1994, encompasses the use of the same aminomethylchroman
- 20 derivatives for the inhibition of HIV-protease.
- DE-2,400,094, published on 18 July 1974, discloses 1-[1-[2-(1,4-benzodioxan-2-yl)-2-hydroxyethyl]-4-piperidyl-2-benzimidazolinones possessing blood pressure lowering activity.
- 25 DE-2,852,945, published on 26 June 1980, discloses benzodioxanylhdroxyethylpiperidylimidazolidinones having antihypertensive activity.
- EP-0,004,358, published on 3 October 1979, discloses *N*-oxacycloalkylalkylpiperidines
- 30 useful as antidepressants and psychostimulants.
- EP-0,048,218, published on 24 March 1982, discloses *N*-oxides of *N*-oxacycloalkylalkylpiperidines having antidepressant activity.
- 35 WO-93/17017, published on 2 September 1993, discloses [(benzodioxane, benzofuran or benzopyran)alkylamino]alkyl-substituted guanidine as selective vasoconstrictors useful to treat conditions related to vasodilatation such as, e.g., migraine, cluster headache and headache associated with vascular disorders.

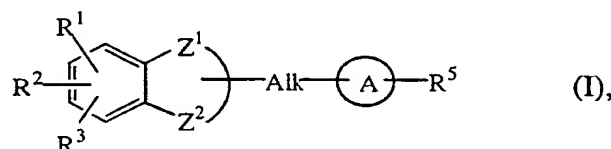
WO-95/053837, published on 23 February 1995, encompasses dihydrobenzopyran-pyrimidine derivatives also having vasoconstrictive activity.

Other structurally related aminomethylchroman derivatives are disclosed in
 5 WO-97/28157, published on 7 August 1997, as α_2 -adrenergic receptor antagonists useful in the treatment of degenerative neurological conditions.

The compounds of the present invention differ from the cited art-known compounds structurally, by the nature of the R⁵ substituent, and pharmacologically by the fact that,
 10 unexpectedly, these compounds have fundic relaxation properties. Furthermore, the compounds of the present invention have additional beneficial pharmacological properties in that they have little or no vasoconstrictor activity.

During the consumption of a meal the fundus, *i.e.* the proximal part of the stomach,
 15 relaxes and provides a "reservoir" function. Patients having an impaired adaptive relaxation of the fundus upon food ingestion have been shown to be hypersensitive to gastric distension and display dyspeptic symptoms. Therefore, it is believed that compounds which are able to normalize an impaired fundic relaxation are useful to
 20 relieve patients suffering from said dyspeptic symptoms.

The present invention concerns compounds of formula (I)



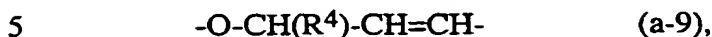
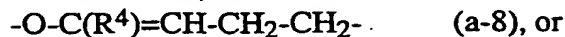
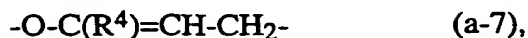
25 a stereochemically isomeric form thereof, an *N*-oxide form thereof, a pharmaceutically acceptable acid addition salt thereof, or a quaternary ammonium salt thereof, wherein Alk is C₁₋₄alkylcarbonyl, C₁₋₄alkylcarbonylC₁₋₄alkyl, carbonyl, carbonylC₁₋₄alkyl, or C₁₋₆alkanediyl optionally substituted with hydroxy, halo, amino, hydroxyC₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkylcarbonyloxy,
 30 C₁₋₄alkylcarbonyloxyC₁₋₄alkyloxy, or C₃₋₆cycloalkylcarbonyloxyC₁₋₄alkyloxy; -Z¹-Z²- is a bivalent radical of formula

-O-CH(R⁴)-CH₂- (a-1),

-O-CH(R⁴)-CH₂-O- (a-2),

35 -O-CH(R⁴)-CH₂-S- (a-3),

-O-CH(R⁴)-CH₂-CH₂- (a-4),



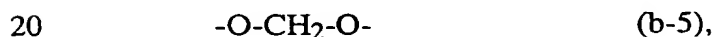
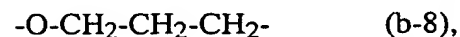
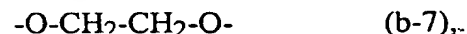
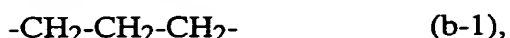
wherein optionally one or two hydrogen atoms on the same or a different carbon atom may be replaced by hydroxy;

R^1 , R^2 and R^3 are each independently selected from hydrogen, C_{1-6} alkyl, C_{3-6} alkenyl,

C_{1-6} alkyloxy, trihalomethyl, trihalomethoxy, halo, hydroxy, cyano, nitro, amino, C_{1-6} alkylcarbonylamino, C_{1-6} alkyloxycarbonyl, C_{1-4} alkylcarbonyloxy, aminocarbonyl, mono- or di(C_{1-6} alkyl)aminocarbonyl, amino C_{1-6} alkyl, mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyl, C_{1-4} alkylcarbonyloxy C_{1-4} alkyloxycarbonyloxy, or C_{3-6} cycloalkylcarbonyloxy C_{1-4} alkyloxycarbonyloxy; or

when R^1 and R^2 are on adjacent carbon atoms, R^1 and R^2 taken together may form a


15 bivalent radical of formula

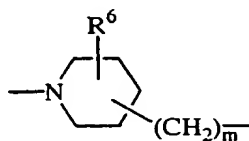


wherein optionally one or two hydrogen atoms on the same or a different carbon atom may be replaced by hydroxy, C_{1-4} alkyl or CH_2OH ;

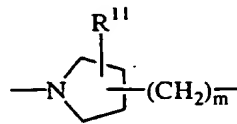
R^4 is hydrogen, C_{1-6} alkyl, phenylmethyl, hydroxy C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl,

C_{1-4} alkyloxycarbonyl, C_{1-4} alkylcarbonyloxy C_{1-4} alkyloxycarbonyl, C_{3-6} cycloalkylcarbonyloxy C_{1-4} alkyloxycarbonyloxy, or a direct bond when the bivalent radical $-\text{Z}^1-\text{Z}^2-$ is of formula (a-6), (a-7) or (a-8);

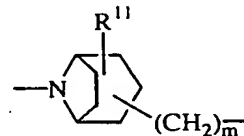
 is a bivalent radical of formula



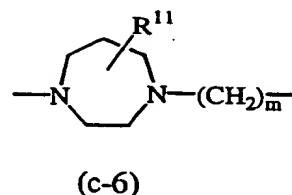
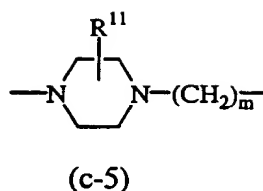
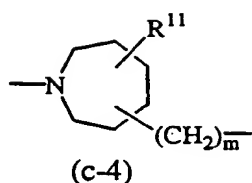
(c-1)



(c-2)



(c-3)

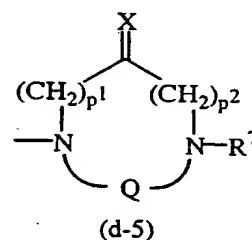
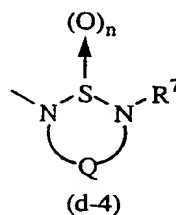
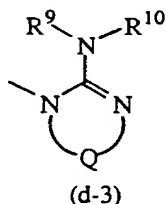
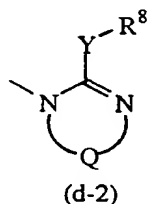
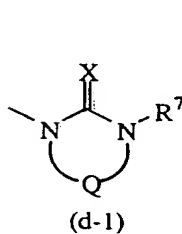


wherein m is 0 or 1;

R⁶ is C₁₋₄alkyl, halo, hydroxy, hydroxyC₁₋₄alkyl, C₁₋₄alkyloxy, aminoC₁₋₄alkyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxyC₁₋₄alkyloxycarbonyl, or C₃₋₆cycloalkylcarbonyloxyC₁₋₄alkyloxycarbonyloxy;

R¹¹ is hydrogen, C₁₋₄alkyl, halo, hydroxy, hydroxyC₁₋₄alkyl, C₁₋₄alkyloxy, aminoC₁₋₄alkyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxyC₁₋₄alkyloxycarbonyl, or C₃₋₆cycloalkylcarbonyloxyC₁₋₄alkyloxycarbonyloxy;

R⁵ is a radical of formula



wherein n is 1 or 2;

p¹ is 0, and p² is 1 or 2; or p¹ is 1 or 2, and p² is 0;

X is oxygen, sulfur, NR⁹ or CHNO₂;

Y is oxygen or sulfur;

R⁷ is hydrogen, C₁₋₆alkyl, C₃₋₆cycloalkyl, phenyl or phenylmethyl;

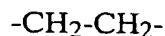
R⁸ is C₁₋₆alkyl, C₃₋₆cycloalkyl, phenyl or phenylmethyl;

R⁹ is cyano, C₁₋₆alkyl, C₃₋₆cycloalkyl, C₁₋₆alkyloxycarbonyl or aminocarbonyl;

R¹⁰ is hydrogen or C₁₋₆alkyl;

or R⁹ and R¹⁰ taken together with the nitrogen atom to which they are attached may form a pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, or morpholinyl group, optionally substituted with C₁₋₄alkyl or C₁₋₄alkyloxy; and

Q is a bivalent radical of formula



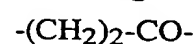
(e-1),



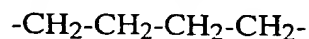
(e-6),



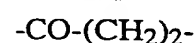
(e-2),



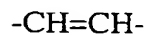
(e-7),



(e-3),



(e-8),



(e-4),



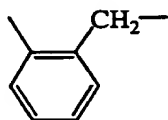
(e-9),

-5-

-CH₂-CO- (e-5), -CH₂-CO-CH₂- (e-10),

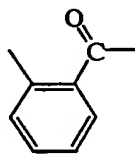
wherein optionally one or two hydrogen atoms on the same or a different carbon atom may be replaced by C₁₋₄alkyl, hydroxy or phenyl, or

Q is a bivalent radical of formula



(e-11)

, or



(e-12)

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As used in the foregoing definitions halo is generic to fluoro, chloro, bromo and iodo; C₁₋₄alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, 1-methyl-ethyl, 2-methylpropyl and the like; C₁₋₆alkyl is meant to include C₁₋₄alkyl and the higher homologues thereof having 5 or 6 carbon atoms, such as, for example, 2-methyl-butyl, pentyl, hexyl and the like; C₃₋₆cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; C₃₋₆alkenyl defines straight and branched chain unsaturated hydrocarbon radicals having from 3 to 6 carbon atoms, such as propenyl, butenyl, pentenyl or hexenyl; C₁₋₂alkanediyl defines methylene or 1,2-ethanediyl; C₁₋₅alkanediyl defines bivalent straight or branched chain hydrocarbon radicals containing from 1 to 5 carbon atoms such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl, and the branched isomers thereof; C₁₋₆alkanediyl includes C₁₋₅alkanediyl and the higher homologues thereof having 6 carbon atoms such as, for example, 1,6-hexanediyl and the like. The term "CO" refers to a carbonyl group.

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In compounds of formula (I) wherein the bivalent radical -Z¹-Z²- is of formula (a-6), (a-7) or (a-8) the substituent R⁴ is a direct bond to the -Alk-(A)-R⁵ moiety.

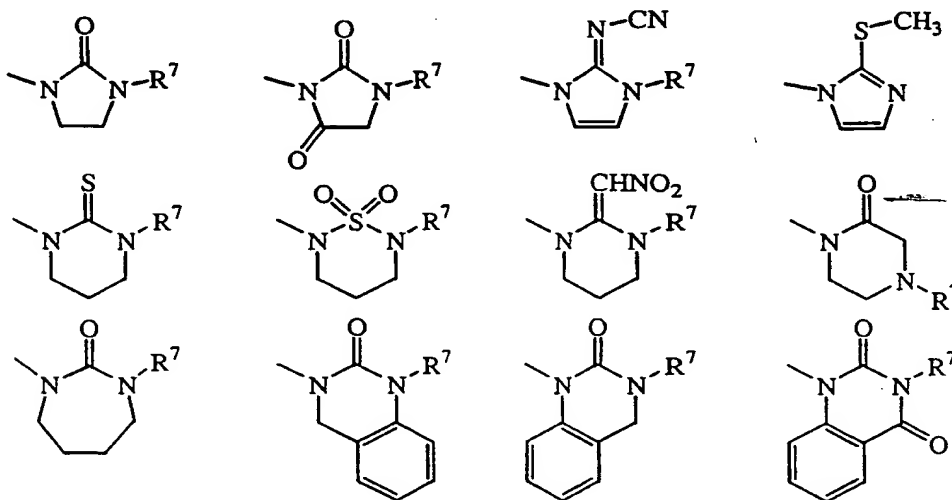
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The term "stereochemically isomeric forms" as used hereinbefore defines all the possible isomeric forms which the compounds of formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centers may have the R- or S-configuration; substituents on bivalent cyclic (partially) saturated radicals may have either the cis- or trans-configuration. Compounds encompassing double bonds can have an E or Z-stereochemistry at said

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double bond. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be embraced within the scope of this invention. The tropane moiety (b-3) can have either an endo- or an exo-configuration.

- 5 Some examples of the R^5 moiety are :



- 10 The pharmaceutically acceptable acid addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The pharmaceutically acceptable acid addition salts can conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as
- 15 hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (*i.e.* ethanedioic), malonic, succinic (*i.e.* butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and
- 20 the like acids.

Conversely said salt forms can be converted by treatment with an appropriate base into the free base form.

- 25 Quaternary ammonium salts of compounds of formula (I) as used herein defines which the compounds of formula (I) are able to form by reaction between a basic nitrogen of a compound of formula (I) and an appropriate quaternizing agent, such as, for example, an optionally substituted alkylhalide, arylhalide or arylalkylhalide, e.g. methyl iodide or benzyliodide. Other reactants with good leaving groups may also be used, such as alkyl

trifluoromethanesulfonates, alkyl methanesulfonates, and alkyl p-toluenesulfonates. A quaternary ammonium salt has a positively charged nitrogen. Pharmaceutically acceptable counterions include chloro, bromo, iodo, trifluoroacetate and acetate. The counterion of choice can be made using ion exchange resin columns.

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The term addition salt as used hereinabove also comprises the solvates which the compounds of formula (I) as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like.

- 10 The *N*-oxide forms of the compounds of formula (I), which may be prepared in art-known manners, are meant to comprise those compounds of formula (I) wherein the nitrogen atom in the bivalent radical of formula $\text{---}\text{A}\text{---}$ is oxidized to the *N*-oxide.

15 Interesting compounds are those compounds of formula (I) wherein one or more of the following restrictions apply :

- a) the bivalent radical $\text{---Z}^1\text{---Z}^2\text{---}$ is of formula (a-1), or (a-6); or
- b) the bivalent radical $\text{---Z}^1\text{---Z}^2\text{---}$ is of formula (a-2), (a-3), (a-4), or (a-9); in particular the bivalent radical $\text{---Z}^1\text{---Z}^2\text{---}$ is of formula (a-3) or (a-4); or
- c) the bivalent radical $\text{---Z}^1\text{---Z}^2\text{---}$ is of formula (a-4);
- 20 d) R^1 , R^2 and R^3 are each independently selected from hydrogen, C_{1-6} alkyl, hydroxy or halo;
- e) R^4 is hydrogen;
- f) Alk is C_{1-2} alkanediyl, in particular Alk is $\text{---CH}_2\text{---}$; or Alk is C_{1-2} alkanediyl substituted with hydroxy;
- 25 g) the bivalent radical $\text{---}\text{A}\text{---}$ is of formula (c-1) wherein R^6 is hydroxy, methoxy, or hydroxymethyl, and $m = 0$, or of formula (c-2) and $m = 0$.

Particular compounds are those compounds of formula (I) wherein R^5 is a radical of formula (d-1) wherein X is oxygen, and Q is a radical of formula (e-1) or (e-2).

30

Preferred compounds are those compounds of formula (I) wherein R^4 is hydrogen; $\text{---Z}^1\text{---Z}^2\text{---}$ is of formula $\text{---CH}_2\text{---CH}_2\text{---}$ (a-4), Alk is $\text{---CH}_2\text{---}$; the bivalent radical $\text{---}\text{A}\text{---}$ is of formula (c-1) wherein R^{11} is hydroxy or methoxy and $m = 0$; and R^5 is a radical of formula (d-1) wherein X is oxygen, R^7 is hydrogen, and Q is (e-2).

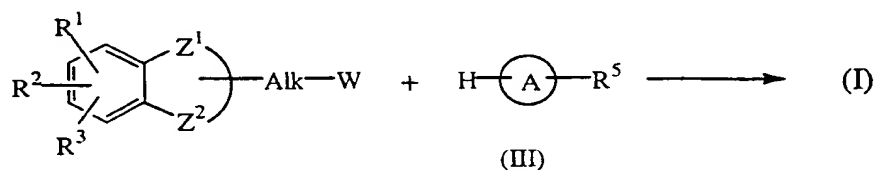
35

Other preferred compounds are those compounds of formula (I) wherein R^4 is hydrogen; $\text{---Z}^1\text{---Z}^2\text{---}$ is of formula $\text{---CH}_2\text{---CH}_2\text{---}$ (a-4), Alk is $\text{---CH}_2\text{---}$; the bivalent radical

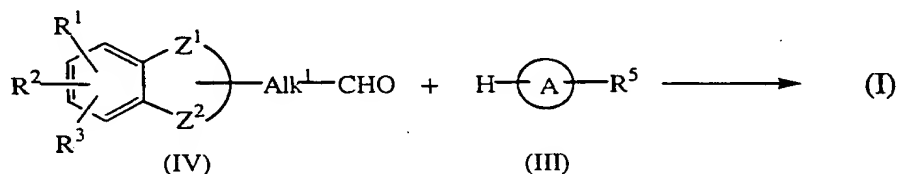
— \bigcirc (A)— is of formula (c-2) and $m = 0$; and R^5 is a radical of formula (d-1) wherein X is oxygen, R^7 is hydrogen, and Q is (e-2).

5 Still other preferred compounds are those compounds of formula (I) wherein R^4 is hydrogen; $-Z^1-Z^2-$ is of formula $-\text{CH}_2-\text{CH}_2-$ (a-4), Alk is $-\text{CH}(\text{OH})-\text{CH}_2-$; the bivalent radical — \bigcirc (A)— is of formula (c-1), $m = 0$, R^6 is hydroxy or hydroxymethyl; and R^5 is a radical of formula (d-1) wherein X is oxygen, R^7 is hydrogen, and Q is (e-2).

10 The compounds of the present invention can generally be prepared by alkylating an intermediate of formula (III) with an intermediate of formula (II), wherein ~~W~~ is an appropriate leaving group such as, for example, halo, e.g. fluoro, chloro, bromo, iodo, or in some instances W may also be a sulfonyloxy group, e.g. methanesulfonyloxy, benzenesulfonyloxy, trifluoromethanesulfonyloxy and the like reactive leaving groups. The reaction can be performed in a reaction-inert solvent such as, for example, acetonitrile or tetrahydrofuran, and optionally in the presence of a suitable base such as, 15 for example, sodium carbonate, potassium carbonate, calciumoxide or triethylamine. Stirring may enhance the rate of the reaction. The reaction may conveniently be carried out at a temperature ranging between room temperature and the reflux temperature of the reaction mixture and, if desired, the reaction may be carried out in an autoclave at 20 an increased pressure.



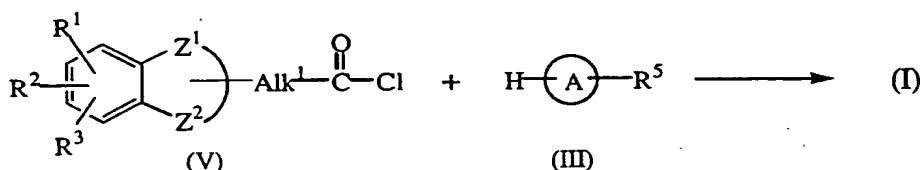
25 Compounds of formula (I) can also be prepared by reductively alkylating an intermediate of formula (IV), wherein Alk^1 represents a direct bond or C_{1-5} alkanediyl, following art-known reductive alkylation procedures with an intermediate (III).



30 Said reductive alkylation can be performed in a reaction-inert solvent such as, for example, dichloromethane, ethanol, toluene or a mixture thereof, and in the presence of a reducing agent such as, for example, a borohydride, e.g. sodium borohydride, sodium

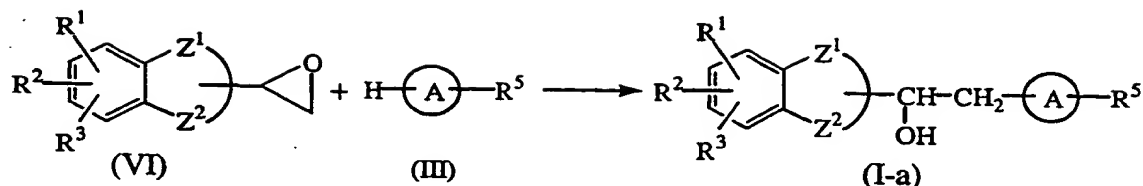
cyanoborohydride or triacetoxy borohydride. It may also be convenient to use hydrogen as a reducing agent in combination with a suitable catalyst such as, for example, palladium-on-charcoal, rhodium-on-carbon or platinum-on-charcoal. In case hydrogen is used as reducing agent, it may be advantageous to add a dehydrating agent to the reaction mixture such as, for example, aluminium *tert*-butoxide. In order to prevent the undesired further hydrogenation of certain functional groups in the reactants and the reaction products, it may also be advantageous to add an appropriate catalyst-poison to the reaction mixture, e.g., thiophene or quinoline-sulphur. To enhance the rate of the reaction, the temperature may be elevated in a range between room temperature and the reflux temperature of the reaction mixture and optionally the pressure of the hydrogen gas may be raised.

Alternatively, compounds of formula (I) can also be prepared by reacting an acid chloride of formula (V), wherein Alk¹ represents C₁₋₅alkanediyl or a direct bond, with an intermediate of formula (III) under suitable reaction conditions.



Said reaction can be performed under hydrogenation conditions with hydrogen gas in the presence of a suitable catalyst such as, for example, palladium-on-charcoal, rhodium-on-carbon or platinum-on-charcoal, in a suitable solvent such as, for example, ethyl acetate, and in the presence of magnesiumoxide. In order to prevent the undesired further hydrogenation of certain functional groups in the reactants and the reaction products, it may also be advantageous to add an appropriate catalyst-poison to the reaction mixture, e.g. thiophene or quinoline-sulphur. To enhance the rate of the reaction, the temperature may be elevated in a range between room temperature and the reflux temperature of the reaction mixture and optionally the pressure of the hydrogen gas may be raised.

30 Compounds of formula (I-a), defined as compounds of formula (I) wherein Alk represents $-\text{CH}(\text{OH})-\text{CH}_2-$, can be prepared by reacting intermediates of formula (VI) with intermediates of formula (III) in a reaction-inert solvent, such as methanol, and optionally in the presence of an anorganic base, such as sodium carbonate.



The compounds of formula (I) may further be prepared by converting compounds of formula (I) into each other according to art-known group transformation reactions.

The compounds of formula (I) may also be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with an appropriate organic or inorganic peroxide.

Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarbo-peroxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzene-carboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. *tert*-butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

The starting materials and some of the intermediates are known compounds and are commercially available or may be prepared according to conventional reaction procedures generally known in the art. For example, a number of intermediates of formula (II) or (V) may be prepared according to art-known methodologies described in WO-93/17017 and WO-95/053837.

Compounds of formula (I) and some of the intermediates may have one or more stereogenic centers in their structure, present in a *R* or a *S* configuration, such as, e.g. the carbon atom bearing the R⁴ substituent, and the carbon atom linked to the -Alk¹-A-R⁵ moiety.

The compounds of formula (I) as prepared in the hereinabove described processes may be synthesized in the form of racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of formula (I) may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently

separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The compounds of formula (I), the *N*-oxide forms, the pharmaceutically acceptable salts and stereoisomeric forms thereof possess favourable fundic relaxation properties as evidenced in pharmacological example C-1, the "Gastric tone measured by an electronic barostat in conscious dogs"-test.

Furthermore, the compounds of the present invention have additional beneficial pharmacological properties in that they have little or no vasoconstrictor activity as can be demonstrated in pharmacological example C.2 "Vasoconstrictive activity on basilar artery". Vasoconstrictor activity can cause undesirable side-effects such as coronary effects which can induce chest pain.

In view of the capability of the compounds of the present invention to relax the fundus, the subject compounds are useful to treat conditions related to a hampered or impaired relaxation of the fundus such as, e.g. dyspepsia, early satiety, bloating and anorexia.

Dyspepsia is described as a motility disorder. Symptoms can be caused by a delayed gastric emptying or by impaired relaxation of the fundus to food ingestion. Warm-blooded animals, including humans, (generally called herein patients) suffering from dyspeptic symptoms as a result of delayed gastric emptying usually have a normal fundic relaxation and can be relieved of their dyspeptic symptoms by administering a prokinetic agent such as, e.g. cisapride. Patients can have dyspeptic symptoms without having a disturbed gastric emptying. Their dyspeptic symptoms may result from a hypercontracted fundus or hypersensitivity resulting in a diminished compliance and abnormalities in the adaptive fundic relaxation. A hypercontracted fundus results in a diminished compliance of the stomach. The "compliance of the stomach" can be expressed as the ratio of the volume of the stomach over the pressure exerted by the stomach wall. The compliance of the stomach relates to the gastric tone, which is the result of the tonic contraction of muscle fibers of the proximal stomach. This proximal

part of the stomach, by exerting a regulated tonic contraction (gastric tone), accomplishes the reservoir function of the stomach.

5 Patients suffering from early satiety cannot finish a normal meal since they feel saturated before they are able to finish said normal meal. Normally when a subject starts eating, the stomach will show an adaptive relaxation, *i.e.* the stomach will relax to accept the food that is ingested. This adaptive relaxation is not possible when the compliance of the stomach is hampered which results in an impaired relaxation of the fundus.

10 In view of the utility of the compounds of formula (I), it follows that the present invention also provides a method of treating warm-blooded animals, including humans, (generally called herein patients) suffering from impaired relaxation of the fundus to food ingestion. Consequently a method of treatment is provided for relieving patients
15 suffering from conditions, such as, for example, dyspepsia, early satiety, bloating and anorexia.

Hence, the use of a compound of formula (I) as medicine is provided, and in particular the use of a compound of formula (I) for the manufacture of a medicine for treating
20 conditions involving an impaired relaxation of the fundus to food ingestion. Both prophylactic and therapeutic treatment are envisaged.

The symptoms of impaired fundic relaxation may also arise due to the intake of chemical substances, *e.g.* Selective Serotonin Re-uptake Inhibitors (SSRI's), such as
25 fluoxetine, paroxetine, fluvoxamine, citalopram and sertraline.

To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, in base or acid addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which
30 carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils,
35 alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most

advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deleterious effect to the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment. Acid addition salts of (I) due to their increased water solubility over the corresponding base form, are obviously more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

For oral administration, the pharmaceutical compositions may take the form of solid dose forms, for example, tablets (both swallowable-only and chewable forms), capsules or gelcaps, prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium phosphate); lubricants e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art.

Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means, optionally with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methylcellulose, hydroxypropyl methylcellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl p-hydroxybenzoates or sorbic acid).

- 5
- 10 Pharmaceutically acceptable sweeteners comprise preferably at least one intense sweetener such as saccharin, sodium or calcium saccharin, aspartame, acesulfame potassium, sodium cyclamate, alitame, a dihydrochalcone sweetener, monellin, stevioside or sucralose (4,1',6'-trichloro-4,1',6'-trideoxygalactosucrose), preferably saccharin, sodium or calcium saccharin, and optionally a bulk sweetener such as
- 15 sorbitol, mannitol, fructose, sucrose, maltose, isomalt, glucose, hydrogenated glucose syrup, xylitol, caramel or honey.

- Intense sweeteners are conveniently employed in low concentrations. For example, in the case of sodium saccharin, the concentration may range from 0.04% to 0.1% (w/v)
- 20 based on the total volume of the final formulation, and preferably is about 0.06% in the low-dosage formulations and about 0.08% in the high-dosage ones. The bulk sweetener can effectively be used in larger quantities ranging from about 10% to about 35%, preferably from about 10% to 15% (w/v).

- 25 The pharmaceutically acceptable flavours which can mask the bitter tasting ingredients in the low-dosage formulations are preferably fruit flavours such as cherry, raspberry, black currant or strawberry flavour. A combination of two flavours may yield very good results. In the high-dosage formulations stronger flavours may be required such as Caramel Chocolate flavour, Mint Cool flavour, Fantasy flavour and the like
- 30 pharmaceutically acceptable strong flavours. Each flavour may be present in the final composition in a concentration ranging from 0.05% to 1% (w/v). Combinations of said strong flavours are advantageously used. Preferably a flavour is used that does not undergo any change or loss of taste and colour under the acidic conditions of the formulation.

35

The compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example,

the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example as a sparingly soluble salt.

- 5 The compounds of the invention may be formulated for parenteral administration by injection, conveniently intravenous, intramuscular or subcutaneous injection, for example by bolus injection or continuous intravenous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multidose containers, with an added preservative. The compositions may take such forms as
- 10 suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as isotoning, suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water before use.
- 15 The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration the compounds of the invention may be used, for

20 example, as a liquid spray, as a powder or in the form of drops.

The formulations of the present invention may optionally include an anti-flatulent, such as simethicone, alpha-D-galactosidase and the like.

- 25 In general it is contemplated that a therapeutically effective amount would be from about 0.001 mg/kg to about 2 mg/kg body weight, preferably from about 0.02 mg/kg to about 0.5 mg/kg body weight. A method of treatment may also include administering the active ingredient on a regimen of between two or four intakes per day.

30 Experimental part

In the procedures described hereinafter the following abbreviations were used : "ACN" stands for acetonitrile; "THF", which stands for tetrahydrofuran; "DCM" stands for dichloromethane; and "MIK" stands for methyl isobutyl ketone.

- 35 For some chemicals the chemical formula was used, e.g. CH_2Cl_2 for dichloromethane, CH_3OH for methanol, NH_3 for ammonia, HCl for hydrochloric acid, NaOH for sodium hydroxide, and Na_2CO_3 sodium carbonate.

In those cases the stereochemically isomeric form which was first isolated is designated as "A" and the second as "B", without further reference to the actual stereochemical configuration.

5 A. Preparation of the intermediates

Example A.1

- 10 a) A mixture of ethyl 3-methoxy-4-oxo-1-piperidinecarboxylate (0.248 mol) and *N,N*-bis(phenylmethyl)-1,3-propanediamine (0.248 mol) in methanol (600 ml) was hydrogenated at 50°C with platinum on activated carbon (5%, 5 g) as a catalyst in the presence of thiophene (4%, 5 ml). After uptake of hydrogen (1 equivalent), the catalyst was filtered off and the filtrate was evaporated, yielding 109.8 g of (±)-ethyl 4-[[3-[bis-(phenylmethyl)amino]propyl]amino]-3-methoxy-1-piperidinecarboxylate (interm. 1).
- 15 b) A mixture of intermediate (1) (0.25 mol) in methanol (500 ml) was hydrogenated at 50°C with palladium on activated carbon (5.0 g) as a catalyst. After uptake of hydrogen (2 equivalents), the catalyst was filtered off and the filtrate was evaporated, yielding 66.3 g (102%) of (±)-ethyl 4-[(3-aminopropyl)amino]-3-methoxy-1-piperidinecarboxylate (interm. 2).
- 20 c) A mixture of intermediate (2) (0.13 mol) and 1,1'-carbonylbis-1*H*-imidazole (0.13 mol) in THF (500 ml) was stirred and refluxed overnight. The solvent was evaporated. The residue was crystallized from ACN. The precipitate was filtered off and dried, yielding 20.0 g of (±)-ethyl 3-methoxy-4-(tetrahydro-2-oxo-1(2*H*)pyrimidinyl)-1-piperidinecarboxylate (interm. 3).
- 25 d) A mixture of intermediate (3) (0.0105 mol) in hydrochloric acid (50 ml) and acetic acid (5 ml) was stirred and refluxed overnight. The solvent was evaporated. The residue was dried, yielding 2.05 g (68%) of (±)-tetrahydro-1-(3-methoxy-4-piperidinyl)-2(1*H*)pyrimidinone dihydrochloride (interm. 4).

Example A.2

- 30 a) A mixture of (S)-1-(phenylmethyl)-3-pyrrolidinamine, (0.115 mol) and 2-propenenitrile (0.115 mol) in ethanol (250 ml) was stirred and refluxed for 2 hours. 2-Propenenitrile (1 g) was added and the reaction mixture was stirred and refluxed for another 2 hours. The solvent was evaporated, yielding 27.0 g of (S)-3-[[1-(phenylmethyl)-3-pyrrolidinyl]amino]propanenitrile (interm. 5).
- 35 b) A mixture of intermediate (5) (max. 0.115 mol) in a solution of ammonia in methanol (400 ml) was hydrogenated at a temperature below 20°C with Raney nickel (3.0 g) as a catalyst. After uptake of hydrogen (2 equivalents), the catalyst was filtered

off and the filtrate was evaporated, yielding 28.0 g of (S)-N-[1-(phenylmethyl)-3-pyrrolidinyl]-1,3-propanediamine (interm. 6).

- 5 c) A mixture of intermediate (6) (0.12 mol) and 1,1'-carbonylbis-1*H*-imidazole (0.12 mol) in THF (500 ml) was stirred and refluxed overnight. The solvent was evaporated, yielding 22.5 g of (S)-1-[1-(phenylmethyl)-3-pyrrolidinyl]-2(1*H*)pyrimidinone (interm. 7).

- 10 d) A mixture of intermediate (7) (0.087 mol) in methanol (400 ml) was hydrogenated with palladium on activated carbon (3.0 g) as a catalyst. After uptake of hydrogen (1 equivalent), the catalyst was filtered off and the filtrate was evaporated, yielding 14.3 g of (S)-1-(3-pyrrolidinyl)-2(1*H*)pyrimidinone (interm. 8).

In an analogous way, (R)-1-(3-pyrrolidinyl)-2(1*H*)pyrimidinone (interm. 9) was prepared.

Example A.3

- 15 a) A mixture of 4-amino-1-(phenylmethyl)-4-piperidinemethanol (0.0182 mol) and 2-propenenitrile (0.0304 mol) in ethanol (80 ml) was stirred and refluxed over the weekend. 2-Propenenitrile (2 ml) was added. The mixture was stirred and refluxed for 5 hours. 2-Propenenitrile (2 ml) was added again. The mixture was stirred and refluxed overnight. The solvent was evaporated. The residue was purified over silica gel on a
20 glass filter (eluent : CH₂Cl₂/(CH₃OH/NH₃) 95/5). The desired fractions were collected and the solvent was evaporated, yielding 3-[[4-(hydroxymethyl)-1-(phenylmethyl)-4-piperidinyl]amino]-propanenitrile (interm. 10).

- b) A mixture of intermediate (10) (0.0159 mol) in methanol saturated with NH₃ (150 ml) was hydrogenated at 14°C with Raney nickel (1/2 spoon) as a catalyst. After
25 uptake of hydrogen (2 equivalents), the catalyst was filtered off and the filtrate was evaporated, yielding 3.8 g of 4-[(3-aminopropyl)amino]-1-(phenylmethyl)-4-piperidine-methanol (interm. 11).

- c) 1,1'-Carbonylbis-1*H*-imidazole (0.0149 mol) was added to a mixture of intermediate (11) (0.0137 mol) in THF (40 ml). The mixture was stirred at room temperature
30 overnight. The precipitate was filtered off, crystallized from ACN, filtered off, washed with ACN and DIPE and then dried, yielding 2.05 g of tetrahydro-1-[4-(hydroxymethyl)-1-(phenylmethyl)-4-piperidinyl]-2(1*H*)-pyrimidinone (interm. 12, mp. 210°C).

- d) A mixture of intermediate (12) (0.0059 mol) in methanol (100 ml) was hydrogenated with palladium on carbon (1 g) as a catalyst. After uptake of hydrogen (1 equivalent),
35 the catalyst was filtered off, the filtrate was evaporated and crystallized from ACN, yielding 0.6g of tetrahydro-1-[4-(hydroxymethyl)-4-piperidinyl]-2(1*H*)-pyrimidinone (interm. 13, mp. 162°C).

Example A.4

- 5 a) A mixture of ethyl 4-(aminomethyl)-4-hydroxy-1-piperidinecarboxylic acid ester (0.0248 mol) and 2-propenenitrile (0.0414 mol) in ethanol (110 ml) was stirred and refluxed for 5 hours. The solvent was evaporated. DCM was added. The solvent was evaporated. Toluene was added. The solvent was evaporated. Again 2-propenenitrile (1.35ml) and ethanol (110 ml) were added. The mixture was stirred and refluxed overnight. 2-Propenenitrile (1.35 ml) was added again. The mixture was stirred and refluxed for two days. The solvent was evaporated, yielding 5.5 g of ethyl 4-[(2-cyanoethyl)amino]methyl]-4-hydroxy-1-piperidinecarboxylate (interm. 14).
- 10 b) A mixture of intermediate (14) (0.0216 mol) in methanol saturated with NH_3 (150 ml) was hydrogenated with Raney nickel (1/2 spoon) as a catalyst. After uptake of hydrogen (2 equivalents), the catalyst was filtered off, the filtrate was evaporated and purified by column chromatography over silica gel (eluent : $\text{CH}_2\text{Cl}_2/(\text{CH}_3\text{OH}/\text{NH}_3)$ 90/10). The desired fractions were collected and the solvent was evaporated, yielding 3.8 g of ethyl 4-[(3-aminopropyl)amino]methyl]-4-hydroxy-1-piperidinecarboxylate (interm. 15).
- 15 c) 1,1'-Carbonylbis-1*H*-imidazole (0.016 mol) was added to a mixture of intermediate (15) (0.0147 mol) in THF (50 ml). The mixture was stirred at room temperature overnight. The solvent was evaporated. Water and DIPE were added. The mixture was separated into its layers. The aqueous layer was extracted with DCM. The organic layer was dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent : $\text{CH}_2\text{Cl}_2/(\text{CH}_3\text{OH}/\text{NH}_3)$ 97/3). The desired fractions were collected and the solvent was evaporated. The residue was taken up in
- 20 DIPE. ACN was added. The mixture was warmed up until complete dissolution and then cooled on an ice-bath. The precipitate was filtered off and dried, yielding 1.5 g of ethyl 4-hydroxy-4-[(tetrahydro-2-oxo-1(2*H*)-pyrimidinyl)methyl]-1-piperidine-carboxylate (interm. 16).
- 25 d) A mixture of intermediate (16) (0.1007 mol) and potassium hydroxide (1.0 mol) in 2-propanol (1200 ml) was stirred and refluxed overnight. The solvent was evaporated. Water was added. The solvent was evaporated partially. DCM was added. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was taken up in ACN. The precipitate was filtered off and dried, yielding tetrahydro-1-[(4-hydroxy-4-piperidinyl)methyl]-2(1*H*)-pyrimidinone (interm. 17).
- 30
- 35

B. Preparation of the final compounds

Example B.1

A mixture of intermediate (4) (0.0072 mol) and (-)-(R)-3,4-dihydro-2*H*-1-benzopyran-2-carboxaldehyde (0.0092 mol) in methanol (100 ml) was hydrogenated with palladium on activated carbon (2 g) as a catalyst in the presence of thiophene (4%, 1 ml). After uptake of hydrogen (1 equivalent), the catalyst was filtered off and the filtrate was evaporated. The residue was partitioned between water and DCM. The biphasic mixture was alkalized with 50% NaOH, then filtered over dicalite, and the biphasic filtrate was separated into its layers. The organic layer was dried, filtered and the solvent was evaporated, to give a residue. This residue was separated and purified by reversed-phase liquid chromatography over RP-18 (BDS, 8 μ m; eluent: (0.5% NH₄OAc in H₂O)/CH₃CN/CH₃OH 63/7/30). Four pure fraction groups were collected and their solvent was evaporated, yielding 0.4 g [1(R),[A-(3 α ,4 α)]-1-[1-[(3,4-dihydro-2*H*-1-benzopyran-2-yl)methyl]-3-methoxy-4-piperidinyl]-2(1*H*)-pyrimidinone (comp. 1), 0.4 g of [1(R),[B-(3 α ,4 α)]-1-[1-[(3,4-dihydro-2*H*-1-benzopyran-2-yl)methyl]-3-methoxy-4-piperidinyl]-2(1*H*)-pyrimidinone (comp. 2), 0.1 g of [1(R),[A-(3 α ,4 α)]-1-[1-[(3,4-dihydro-2*H*-1-benzopyran-2-yl)methyl]-3-hydroxy-4-piperidinyl]-2(1*H*)-pyrimidinone (comp. 3) and 0.1 g of [1(R),[B-(3 α ,4 α)]-1-[1-[(3,4-dihydro-2*H*-1-benzopyran-2-yl)methyl]-3-hydroxy-4-piperidinyl]-2(1*H*)-pyrimidinone (comp. 4).

Example B.2

A mixture of intermediate (9) (0.030 mol) and 3,4-dihydro-2*H*-1-benzopyran-2-carboxaldehyde (0.028 mol) in methanol (100 ml) was hydrogenated at 50°C with palladium on activated carbon (2.0 g) as a catalyst in the presence of thiophene (4%, 1 ml). After uptake of hydrogen (1 equivalent), the catalyst was filtered off and the filtrate was evaporated. This fraction was pre-purified by column chromatography over silica gel (gradient elution with CH₂Cl₂/CH₃OH). The desired fractions were collected and the solvent was evaporated. The residue (\pm 5 g) was separated and purified by chiral column chromatography over Chiralcel OD (eluent : hexane/ethanol 80/20). The two pure fraction groups were collected and their solvent was evaporated, yielding 1.75 g of a first fraction and 1.97 g of [3R(B)]-1-[1-[(3,4-dihydro-2*H*-1-benzopyran-2-yl)methyl]-3-pyrrolidinyl]-2(1*H*)-pyrimidinone (comp. 6). Said first fraction was further purified by column chromatography over RP BDS Spherical silica gel (Hyperprep C18 BDS 120 Å, 8 μ m (Shandon); eluent: [(0.5% NH₄OAc in H₂O)/CH₃CN 90/10]/CH₃OH/CH₃CN 75/25/0; 0/50/50; 0/0/100; 75/25/0), yielding 0.45 g of [3R(A)]-1-[1-[(3,4-dihydro-2*H*-1-benzopyran-2-yl)methyl]-3-pyrrolidinyl]-2(1*H*)-pyrimidinone (comp. 5).

Example B.3

A mixture of intermediate (9) (0.031 mol) and 2*H*-1-benzopyran-3-carboxaldehyde (0.031 mol) in methanol (150 ml) was hydrogenated with palladium on activated carbon (2 g) as a catalyst in the presence of thiophene (4%, 1 ml). After uptake of hydrogen (2 equivalents), the catalyst was filtered off and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH gradient elution). The desired fractions were collected and the solvent was evaporated. The residue was separated into the enantiomers by chiral column chromatography over Chiralcel OD (eluent: hexane/ethanol 50/50) and further purified by reversed-phase high-performance liquid chromatography over RP-18 (eluent: ((0.5% NH₄OAc in H₂O)/CH₃CN 90/10)/ CH₃OH/CH₃CN (0 min) 68/27/5, (24 min) 38/37/25). The purest fractions were collected and the solvent was evaporated. The residue was dried, yielding 0.90 g of (3*R*)-1-[1-[(3,4-dihydro-2*H*-1-benzopyran-3-yl)-methyl]-3-pyrrolidinyl]-2(1*H*)pyrimidinone (comp. 19).

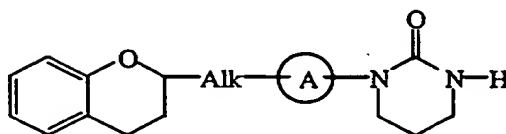
Example B.4


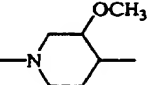
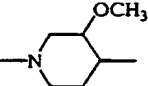
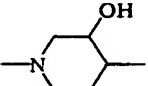
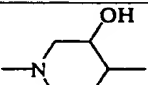
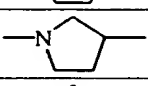
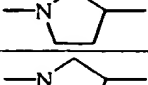
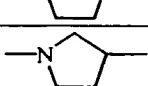

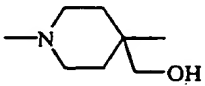
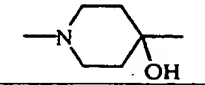



Intermediate (13) (0.0094 mol) was added to a mixture of (R)-3,4-dihydro-2*H*-1-benzopyran-2-methanol methanesulfonate (ester) (0.0094 mol) and Na₂CO₃ (0.0282 mol) in MIK (160 ml). The mixture was stirred and refluxed for a week using a water separator. The solvent was evaporated. Water and DCM were added. The organic layer was separated, washed with water several times, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent : CH₂Cl₂/(CH₃OH/NH₃) 90/10). The desired fractions were collected and the solvent was evaporated. The residue was taken up in ACN. The mixture was heated until complete dissolution and then cooled on an ice-bath. The precipitate was filtered off and dried, yielding 0.3 g of compound (20) (mp. 180°C).

Example B.5

A mixture of [S-(R*,R*)]-3,4-dihydro-2-oxiranyl-2*H*-1-benzopyran (0.0047 mol), intermediate (17) (0.0047 mol) and Na₂CO₃ (0.0042 mol) in ethanol (150 ml) was stirred and refluxed for 2 nights. The solvent was evaporated. Water and DCM were added. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was taken up in a small amount of ACN. The mixture was heated until complete dissolution and then cooled on an ice bath. The precipitate was filtered off and dried, yielding 0.9 g of compound (30).

Table F-1 and F-2 list the compounds that were prepared according to one of the above Examples. The following abbreviations were used in the tables : .C₂H₂O₄ stands for the ethanedioate salt.

5 Table F-1

Co No.	Ex. No.	Alk		physical data mp. in °C
1	B.1	-CH ₂ -		[1(R),[A-(3α,4α)]]; mp. 124.3°C
2	B.1	-CH ₂ -		[1(R),[B-(3α,4α)]]; mp. 158.8°C
3	B.1	-CH ₂ -		[1(R),[A-(3α,4α)]]; mp. 172.1°C
4	B.1	-CH ₂ -		[1(R),[B-(3α,4α)]]; mp. 153.5°C
5	B.2	-CH ₂ -		[3R(A)]
6	B.2	-CH ₂ -		[3R(B)]
7	B.1	-CH ₂ -		[3S(A)]
8	B.1	-CH ₂ -		[3S(B)]
20	B.4	-CH ₂ -		(R); mp. 180°C
21	B.4	-CH ₂ -		(S); mp. 200°C; [α] _D ²⁰ = +74.82° (c = 26.13 mg/5 ml in methanol)
22	B.4	-CH ₂ -		(S); mp. 178°C
23	B.5	-CH(OH)-CH ₂ -		[R-(R*,R*)] + [S-(R*,R*)]
24	B.5	-CH(OH)-CH ₂ -		fraction (B1); mp. 144°C


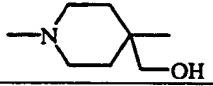

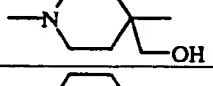
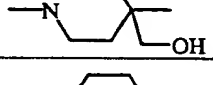
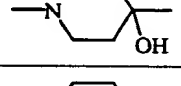
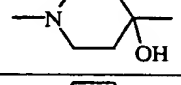
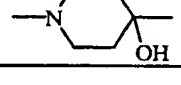
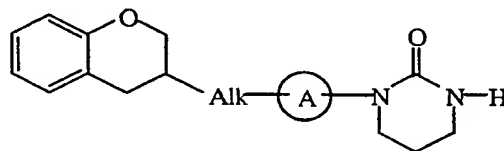
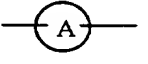
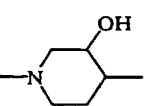
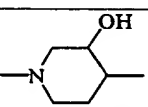
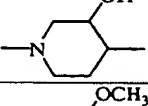
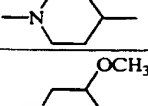
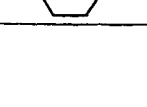

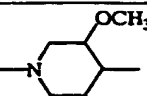
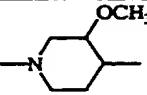
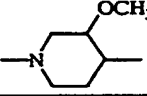

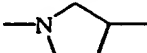
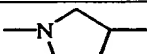
Co No.	Ex. No.	Alk		physical data mp. in °C
25	B.5	-CH(OH)-CH ₂ -		fraction (B2); mp. 90°C
26	B.5	-CH(OH)-CH ₂ -		[R-(R*,S*)] + [S-(R*,S*)]
27	B.5	-CH(OH)-CH ₂ -		fraction (A1); mp. 176°C
28	B.5	-CH(OH)-CH ₂ -		fraction (A2); mp. 176°C
29	B.5	-CH(OH)-CH ₂ -		mp. 182°C; $[\alpha]_D^{20} = -53.68^\circ$ (c = 25.15 mg/5 ml in methanol)
30	B.5	-CH(OH)-CH ₂ -		mp. 182°C; $[\alpha]_D^{20} = +48.91^\circ$ (c = 25.76 mg/5 ml in methanol)
31	B.5	-CH(OH)-CH ₂ -		fraction (A)

Table F-2



5

Co No.	Ex. No.	Alk		physical data (mp. in °C)
9	B.3	-CH ₂ -		[1(A),[A-(3 α ,4 α)]] + [1(B),[A-(3 α ,4 α)]]; mp. 201.8°C; $[\alpha]_D^{20} = +57.11^\circ$ (c = 25.39 mg/5 ml in methanol)
10	B.3	-CH ₂ -		[1(A),[B-(3 α ,4 α)]]; mp. 200.5°C; $[\alpha]_D^{20} = -46.00^\circ$ (c = 25.22 mg/5 ml in methanol)
11	B.3	-CH ₂ -		[1(B),[B-(3 α ,4 α)]]; $[\alpha]_D^{20} = -85.23^\circ$ (c = 26.40 mg/5 ml in methanol)
12	B.3	-CH ₂ -		(CIS)
13	B.3	-CH ₂ -		[1(A),[A-(3 α ,4 α)]]; $[\alpha]_D^{20} = +62.84^\circ$ (c = 5.57 mg/5 ml in DMF)

Co No.	Ex. No.	Alk		physical data (mp. in °C)
14	B.3	-CH ₂ -		[1(B),[A-(3 α ,4 α)]]; [α] _D ²⁰ = +103.63° (c = 5.79 mg/5 ml in DMF)
15	B.3	-CH ₂ -		[1(B),[B-(3 α ,4 α)]]; [α] _D ²⁰ = -54.67° (c = 7.50 mg/5 ml in DMF)
16	B.3	-CH ₂ -		[1(A),[B-(3 α ,4 α)]]; mp. 197°C; [α] _D ²⁰ = -107.35° (c = 6.80 mg/5 ml in DMF)
17	B.3	-CH ₂ -		[3A(3S)]; mp. 126.6°C
18	B.3	-CH ₂ -		[3B(3S)]; mp. 113.2°C
19	B.3	-CH ₂ -		(3R)

C. Pharmacological examples

C.1. Gastric tone measured by an electronic barostat in conscious dogs

Gastric tone cannot be measured by manometric methods. Therefore an electronic barostat was used. This allows the study of the physiological pattern and regulation of gastric tone in conscious dogs and the influence of test-compounds on this tone.

The barostat consists of an air injection system which is connected by a double-lumen 14-French polyvinyl tube to an ultrathin flaccid polyethylene bag (maximal volume: ± 700 ml). Variations in gastric tone were measured by recording changes in the volume of air within an intragastric bag, maintained at a constant pressure. The barostat maintains a constant pressure (preselected) within a flaccid air-filled bag introduced into the stomach, changing the volume of air within the bag by an electronic feedback system.

Thus, the barostat measures gastric motor activity (contraction or relaxation) as changes in intragastric volume (decrease or increase resp.) at a constant intragastric pressure. The barostat consists of a strain gauge linked by an electronic relay to an air injection-aspiration system. Both the strain gauge and the injection system are connected by means of double-lumen polyvinyl tube to an ultrathin polyethylene bag. A dial in the barostat allows selection of the pressure level to be maintained within the intragastric bag.

Female beagle dogs, weighing 7-17 kg, were trained to stand quietly in Pavlov frames. They were implanted with a gastric cannula under general anaesthesia and aseptic precautions. After a median laparotomy, an incision was made through the gastric wall in longitudinal direction between the greater and the lesser curve, 2 cm above the nerves of Latarjet. The cannula was secured to the gastric wall by means of a double purse string suture and brought out via a stub wound at the left quadrant of the hypochondrium. Dogs were allowed a recovery period of two weeks.

At the beginning of the experiment, the cannula was opened in order to remove any gastric juice or food remnants. If necessary, the stomach was cleansed with 40 to 50 ml lukewarm water. The ultrathin bag of the barostat was positioned into the fundus of the stomach through the gastric cannula. In order to ensure easy unfolding of the intragastric bag during the experiment, a volume of 300-400 ml was injected twice into the bag.

When during a stabilisation period of maximum 90 minutes, the gastric volume is stable during 15 minutes at a constant pressure of 6 mmHg (about 0.81 kPa), the test compound was administered subcutaneously (S.C.), or intraduodenally (I.D.). Test compounds were screened, *i.e.* changes in gastric volume were measured, usually at 0.63 mg/kg. Other doses and routes were tested if a test compound was shown to be active during the screening procedure. Table C-1 summarizes the mean maximal change in volume on relaxation of the fundus, during the 1 hour observation period after S.C. or I.D. administration of the test compound (0.63 mg/kg).

Table C-1 :

Co. No.	Route	Maximum change in volume (ml)	Co. No.	Route	Maximum change in volume (ml)
2	S.C.	9	21	S.C.	68
7	I.D.	16	24	S.C.	48
8	I.D.	22	25	S.C.	23
8	S.C.	29	27	S.C.	46
20	I.D.	178	28	S.C.	21
11	I.D.	64	30	I.D.	34
20	S.C.	262	31	I.D.	26

C.2 Vasoconstrictive activity on basilar artery

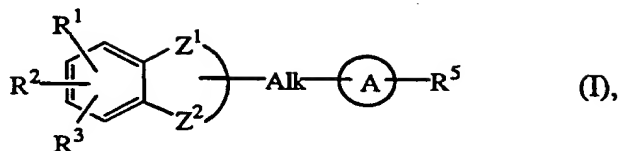
Segments of basilar arteries taken from pigs (anaesthetised with sodium pentobarbital) were mounted for recording of isometric tension in organ baths. The preparations were bathed in Krebs - Henseleit solution. The solution was kept at 37°C and gassed with a mixture of 95% O₂ - 5% CO₂. The preparations were stretched until a stable basal tension of 2 grams was obtained.

The preparations were made to constrict with serotonin (3×10^{-7} M). The response to the addition of serotonin was measured and subsequently the serotonin was washed away. This procedure was repeated until stable responses were obtained. Subsequently the test compound was administered to the organ bath and the constriction of the preparation was measured. This constrictive response was expressed as a percentage of the response to serotonin as measured previously.

The ED₅₀-value (molar concentration) is defined as the concentration at which a test compound causes 50% of the constrictive response obtained with serotonin. Said ED₅₀-values are estimated from experiments on three different preparations.

Claims

1. A compound of formula (I)



a stereochemically isomeric form thereof, an *N*-oxide form thereof, a pharmaceutically acceptable acid addition salt thereof, or a quaternary ammonium salt thereof, wherein

Alk is C₁₋₄alkylcarbonyl, C₁₋₄alkylcarbonylC₁₋₄alkyl, carbonyl, carbonylC₁₋₄alkyl, or C₁₋₆alkanediyl optionally substituted with hydroxy, halo, amino, hydroxyC₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkylcarbonyloxy, C₁₋₄alkylcarbonyloxyC₁₋₄alkyloxy, or C₃₋₆cycloalkylcarbonyloxyC₁₋₄alkyloxy;

-Z¹-Z²- is a bivalent radical of formula

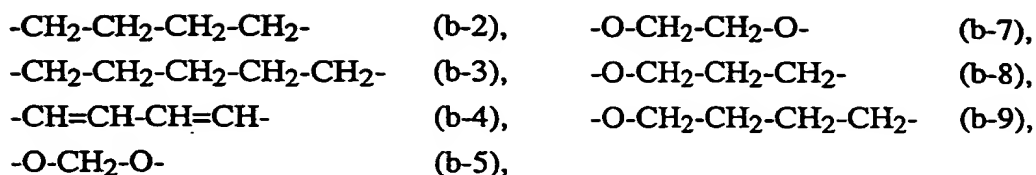
- O-CH(R⁴)-CH₂- (a-1),
- O-CH(R⁴)-CH₂-O- (a-2),
- O-CH(R⁴)-CH₂-S- (a-3),
- O-CH(R⁴)-CH₂-CH₂- (a-4),
- O-CH(R⁴)-CH₂-CH₂-CH₂- (a-5),
- O-C(R⁴)=CH- (a-6),
- O-C(R⁴)=CH-CH₂- (a-7),
- O-C(R⁴)=CH-CH₂-CH₂- (a-8), or
- O-CH(R⁴)-CH=CH- (a-9),

wherein optionally one or two hydrogen atoms on the same or a different carbon atom may be replaced by hydroxy;

R¹, R² and R³ are each independently selected from hydrogen, C₁₋₆alkyl, C₃₋₆alkenyl, C₁₋₆alkyloxy, trihalomethyl, trihalomethoxy, halo, hydroxy, cyano, nitro, amino, C₁₋₆alkylcarbonylamino, C₁₋₆alkyloxy, C₁₋₄alkylcarbonyloxy, aminocarbonyl, mono- or di(C₁₋₆alkyl)aminocarbonyl, aminoC₁₋₆alkyl, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, C₁₋₄alkylcarbonyloxy, C₁₋₄alkyloxy, or C₃₋₆cycloalkylcarbonyloxyC₁₋₄alkyloxy;

when R¹ and R² are on adjacent carbon atoms, R¹ and R² taken together may form a bivalent radical of formula

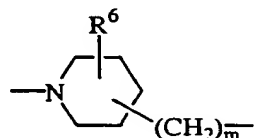
- CH₂-CH₂-CH₂- (b-1),
- O-CH₂-CH₂- (b-6),



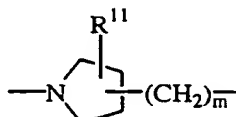
5 wherein optionally one or two hydrogen atoms on the same or a different carbon atom may be replaced by hydroxy, C₁₋₄alkyl or CH₂OH;

R⁴ is hydrogen, C₁₋₆alkyl, phenylmethyl, hydroxyC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxyC₁₋₄alkyloxycarbonyl, C₃₋₆cycloalkylcarbonyloxyC₁₋₄alkyloxycarbonyloxy, or a direct bond when the
10 bivalent radical -Z¹-Z²- is of formula (a-6), (a-7) or (a-8);

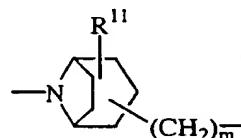
—(A)— is a bivalent radical of formula



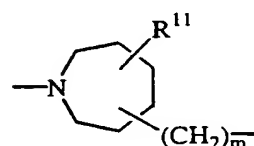
(c-1)



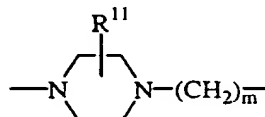
(c-2)



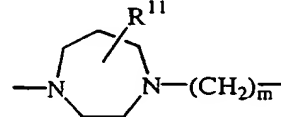
(c-3)



(c-4)



(c-5)



(c-6)

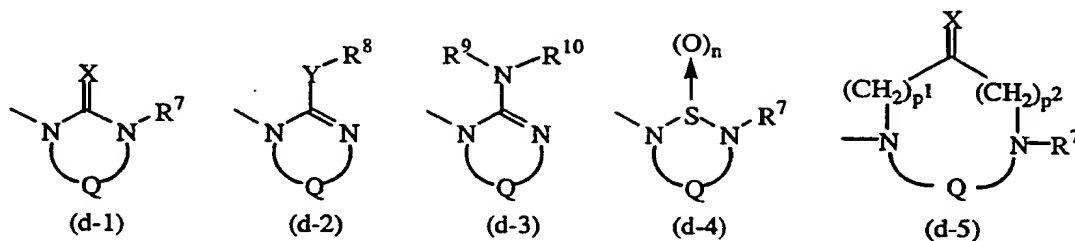
15

wherein m is 0 or 1;

R⁶ is C₁₋₄alkyl, halo, hydroxy, hydroxyC₁₋₄alkyl, C₁₋₄alkyloxy, aminoC₁₋₄alkyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxyC₁₋₄alkyloxycarbonyl, or
20 C₃₋₆cycloalkylcarbonyloxyC₁₋₄alkyloxycarbonyloxy;

R¹¹ is hydrogen, C₁₋₄alkyl, halo, hydroxy, hydroxyC₁₋₄alkyl, C₁₋₄alkyloxy, aminoC₁₋₄alkyl, C₁₋₄alkyloxycarbonyl, C₁₋₄alkylcarbonyloxyC₁₋₄alkyloxycarbonyl, or
C₃₋₆cycloalkylcarbonyloxyC₁₋₄alkyloxycarbonyloxy;

R⁵ is a radical of formula



wherein n is 1 or 2;

5 p¹ is 0, and p² is 1 or 2; p¹ is 1 or 2, and p² is 0;

X is oxygen, sulfur, NR⁹ or CHNO₂;

Y is oxygen or sulfur;

R⁷ is hydrogen, C₁₋₆alkyl, C₃₋₆cycloalkyl, phenyl or phenylmethyl;

R⁸ is C₁₋₆alkyl, C₃₋₆cycloalkyl, phenyl or phenylmethyl;

10 R⁹ is cyano, C₁₋₆alkyl, C₃₋₆cycloalkyl, C₁₋₆alkyloxy carbonyl or aminocarbonyl;

R¹⁰ is hydrogen or C₁₋₆alkyl;

or R⁹ and R¹⁰ taken together with the nitrogen atom to which they are attached may form a pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, or morpholinyl group, optionally substituted with C₁₋₄alkyl or C₁₋₄alkyloxy; and

15 Q is a bivalent radical of formula

-CH₂-CH₂- (e-1),

-CH₂-CH₂-CH₂- (e-2),

-CH₂-CH₂-CH₂-CH₂- (e-3),

20 -CH=CH- (e-4),

-CH₂-CO- (e-5),

-CO-CH₂- (e-6),

-(CH₂)₂-CO- (e-7),

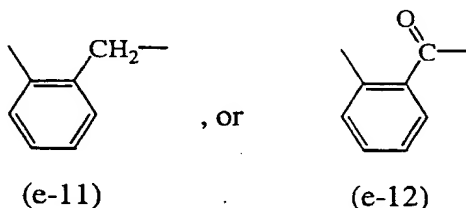
-CO-(CH₂)₂- (e-8),

-CO-CH₂-CO- (e-9),

-CH₂-CO-CH₂- (e-10),

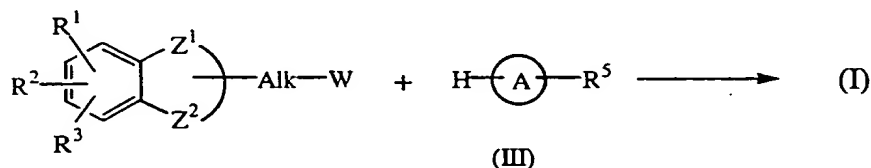
wherein optionally one or two hydrogen atoms on the same or a different carbon atom may be replaced by C₁₋₄alkyl, hydroxy or phenyl, or

25 Q is a bivalent radical of formula



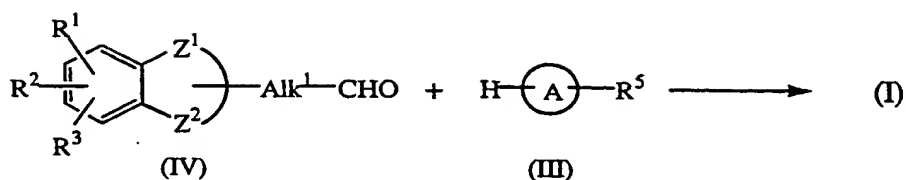
2. A compound as claimed in claim 1 wherein R⁵ is a radical of formula (d-1) wherein X is oxygen, and Q is a radical of formula (e-1) or (e-2).

3. A compound as claimed in claim 1 R^4 is hydrogen; $-Z^1-Z^2-$ is of formula $-\text{CH}_2-\text{CH}_2-$ (a-4), Alk is $-\text{CH}_2-$; the bivalent radical $-\text{A}-$ is of formula (c-1) wherein R^{11} is hydroxy or methoxy and $m = 0$; and R^5 is a radical of formula (d-1) wherein X is oxygen, R^7 is hydrogen, and Q is (e-2).
- 5
4. A compound according to claim 1 wherein R^4 is hydrogen; $-Z^1-Z^2-$ is of formula $-\text{CH}_2-\text{CH}_2-$ (a-4), Alk is $-\text{CH}_2-$; the bivalent radical $-\text{A}-$ is of formula (c-2) and $m = 0$; and R^5 is a radical of formula (d-1) wherein X is oxygen, R^7 is hydrogen, and Q is (e-2).
- 10
5. A compound according to claim 1 wherein R^4 is hydrogen; $-Z^1-Z^2-$ is of formula $-\text{CH}_2-\text{CH}_2-$ (a-4), Alk is $-\text{CH}(\text{OH})-\text{CH}_2-$; the bivalent radical $-\text{A}-$ is of formula (c-1), $m = 0$, R^6 is hydroxy or hydroxymethyl; and R^5 is a radical of formula (d-1) wherein X is oxygen, R^7 is hydrogen, and Q is (e-2).
- 15
6. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically active amount of a compound as claimed in any of claims 1 to 5.
7. A process for preparing a pharmaceutical composition as claimed in claim 6 wherein a therapeutically active amount of a compound as claimed in any of claims 1 to 5 is intimately mixed with a pharmaceutically acceptable carrier.
- 20
8. A compound as claimed in any of claims 1 to 5 for use as a medicine.
- 25
9. A process for preparing a compound of formula (I) wherein
- a) an intermediate of formula (II) is alkylated with an intermediate of formula (III) in a reaction-inert solvent and, optionally in the presence of a suitable base,



30

- b) an intermediate of formula (IV), wherein $\text{Alk}^{1'}$ represents a direct bond or C_{1-5} alkanediyl, is reductively alkylated with an intermediate of formula (III);



wherein in the above reaction schemes the radicals $\text{---Z}^1\text{---Z}^2\text{---}$, R^1 , R^2 , R^3 , R^4 , R^5 , Alk and the bivalent radical $\text{---} \textcircled{\text{A}} \text{---}$ are as defined in claim 1 and W is an

5 appropriate leaving group;

- c) or, compounds of formula (I) are converted into each other following art-known transformation reactions; or if desired; a compound of formula (I) is converted into an acid addition salt, or conversely, an acid addition salt of a compound of formula (I) is converted into a free base form with alkali; and, if desired,
- 10 preparing stereochemically isomeric forms thereof.

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/EP 00/04747

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D405/14 C07D405/12 A61K31/505 A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM. ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 28157 A (PIERRE FABRE) 7 August 1997 (1997-08-07) cited in the application page 18 -page 25	1-3,5-9
A	US 5 696 136 A (H.-G. HEINE ET AL.) 9 December 1997 (1997-12-09) column 1 -column 24	1-3,5-9
A	DE 28 52 945 A (BOEHRINGER) 26 June 1980 (1980-06-26) cited in the application page 1 -page 12	1-3,5-9
A	EP 0 048 218 A (CIBA-GEIGY) 24 March 1982 (1982-03-24) cited in the application claims; examples 1,2	1-3,5-9
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

4 July 2000

Date of mailing of the international search report

13/07/2000

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Fax: (+31-70) 340-3016

Authorized officer

Francois, J

INTERNATIONAL SEARCH REPORT

Internat'l Application No

PCT/EP 00/04747

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 068 261 A (HOECHST) 5 January 1983 (1983-01-05) claims	1-3, 5-9
P, A	WO 99 29687 A (JANSSEN) 17 June 1999 (1999-06-17) the whole document	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/04747

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9728157	A	07-08-1997	FR 2744451 A AU 1606197 A	08-08-1997 22-08-1997
US 5696136	A	09-12-1997	DE 4140540 A US 5545643 A AT 136030 T AU 650182 B AU 2993892 A CA 2084542 A CZ 283680 B DE 59205846 D DK 546388 T EP 0546388 A ES 2086623 T FI 925549 A GR 3019450 T HU 65427 A IL 104006 A JP 5279357 A MX 9206817 A NO 303174 B NZ 245381 A RU 2089549 C SK 361392 A US 5693653 A US 5696137 A US 5371094 A ZA 9209498 A	17-06-1993 13-08-1996 15-04-1996 09-06-1994 10-06-1993 10-06-1993 17-06-1998 02-05-1996 29-07-1996 16-06-1993 01-07-1996 10-06-1993 30-06-1996 28-06-1994 18-02-1997 26-10-1993 30-06-1994 08-06-1998 28-03-1995 10-09-1997 10-09-1997 02-12-1997 09-12-1997 06-12-1994 10-06-1993
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EP 68261	A	05-01-1983	DE 3124366 A AT 12498 T AU 551182 B AU 8499282 A CA 1175432 A DE 3262861 D DK 275782 A ES 513102 D ES 8304974 A FI 822178 A GR 76502 A HU 190989 B IE 53127 B IL 66084 A	30-12-1982 15-04-1985 17-04-1986 06-01-1983 02-10-1984 09-05-1985 21-12-1982 16-03-1983 16-06-1983 21-12-1982 10-08-1984 28-12-1986 06-07-1988 31-07-1986

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/04747

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		MX 155328 A	19-02-1988
		NO 822041 A	21-12-1982
		NZ 201006 A	13-12-1985
		PH 18536 A	09-08-1985
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		US 4470989 A	11-09-1984
		ZA 8204328 A	27-04-1983
WO 9929687 A	17-06-1999	AU 2412799 A	28-06-1999

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES

IPK 7 C07D405/14 C07D405/12 A61K31/505 A61P9/00

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B. RECHERCHIERTE GEBIETE

Recherchierte Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)

IPK 7 C07D A61K A61P

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

CHEM ABS Data

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
A	WO 97 28157 A (PIERRE FABRE) 7. August 1997 (1997-08-07) in der Anmeldung erwähnt Seite 18 -Seite 25 ---	1-3,5-9
A	US 5 696 136 A (H.-G. HEINE ET AL.) 9. Dezember 1997 (1997-12-09) Spalte 1 -Spalte 24 ---	1-3,5-9
A	DE 28 52 945 A (BOEHRINGER) 26. Juni 1980 (1980-06-26) in der Anmeldung erwähnt Seite 1 -Seite 12 ---	1-3,5-9
A	EP 0 048 218 A (CIBA-GEIGY) 24. März 1982 (1982-03-24) in der Anmeldung erwähnt Ansprüche; Beispiele 1,2 ---	1-3,5-9
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☒ Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen☒ Siehe Anhang Patentfamilie

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Bevollmächtigter Bediensteter

Francois, J

INTERNATIONALE RECHERCHENBERICHT

Internationales Aktenzeichen

PCT/EP 00/04747

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
A	EP 0 068 261 A (HOECHST) 5. Januar 1983 (1983-01-05) Ansprüche	1-3,5-9
P,A	WO 99 29687 A (JANSSEN) 17. Juni 1999 (1999-06-17) das ganze Dokument	1-9

INTERNATIONALER RESEARCHENBERICHT

Angaben zu Veröffentlichung... die zur selben Patentfamilie gehören

Internationales Aktenzeichen

PCT/EP 00/04747

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INTERNATIONALER RESEARCHENBERICHT

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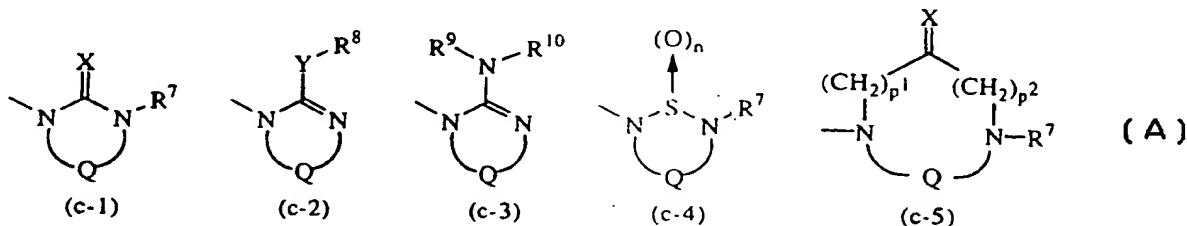
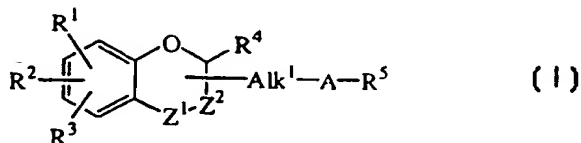
Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
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		MX 155328 A	19-02-1988
		NO 822041 A	21-12-1982
		NZ 201006 A	13-12-1985
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		PT 75070 A, B	01-07-1982
		US 4470989 A	11-09-1984
		ZA 8204328 A	27-04-1983
WO 9929687 A	17-06-1999	AU 2412799 A	28-06-1999



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 405/14, 405/12, 417/12, A61K 31/495	A1	(11) International Publication Number: WO 99/29687 (43) International Publication Date: 17 June 1999 (17.06.99)
(21) International Application Number: PCT/EP98/07771 (22) International Filing Date: 27 November 1998 (27.11.98) (30) Priority Data: 97203808.7 5 December 1997 (05.12.97) EP (71) Applicant (for all designated States except US): JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE). (72) Inventors; and (75) Inventors/Applicants (for US only): WIGERINCK, Piet, Tom, Bert, Paul [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). VERSCHUEREN, Wim, Gaston [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). SCHROVEN, Marc, Francis, Josephine [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). DE BRUYN, Marcel, Frans, Leopold [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). (74) Agent: QUAGHEBEUR, Luc; Janssen Pharmaceutica N.V., Patent Dept., Turnhoutseweg 30, B-2340 Beerse (BE).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>

(54) Title: (BENZODIOXAN, BENZOFURAN OR BENZOPYRAN) DERIVATIVES HAVING FUNDIC RELAXATION PROPERTIES



(57) Abstract

The present invention of compounds of formula (I), a stereochemically isomeric form thereof, an *N*-oxide form thereof or a pharmaceutically acceptable acid addition salt thereof, wherein Alk^1 is C_{1-6} alkanediyl optionally substituted with hydroxy, C_{1-6} alkyloxy or C_{1-6} alkylcarbonyloxy; $-\text{Z}^1-\text{Z}^2-$ is a bivalent radical; R^1 , R^2 and R^3 are each independently selected from hydrogen, C_{1-6} alkyl, hydroxy, halo and the like; or when R^1 and R^2 are on adjacent carbon atoms, R^1 and R^2 taken together may form a bivalent radical; R^4 is hydrogen or C_{1-6} alkyl; A is a bivalent radical of formula $-\text{NR}^6-\text{Alk}^2-(b-1)$, or $-\text{NpiperidinyI}-(\text{CH}_2)_m(b-2)$ wherein m is 0 or 1; R^5 is a radical of formula (A), wherein n is 1 or 2; p^1 is 0, and p^2 is 1 or 2; or p^1 is 1 or 2, and p^2 is 0; X is oxygen, sulfur or $=\text{NR}^9$; Y is oxygen or sulfur; R^7 is hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl or phenylmethyl; R^8 is C_{1-6} alkyl, C_{3-6} cycloalkyl phenyl or phenylmethyl; R^9 is cyano, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkyloxycarbonyl or aminocarbonyl; R^{10} is hydrogen or C_{1-6} alkyl; and Q is a bivalent radical. Processes for preparing said products, formulations comprising said products and their use as a medicine are disclosed, in particular for treating conditions which are related to impaired fundic relaxation.

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CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
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CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

PATENT COOPERATION TREATY

PCT

REC'D 04 APR 2001

WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference JAB 1488-PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP00/04747	International filing date (day/month/year) 23/05/2000	Priority date (day/month/year) 02/06/1999
International Patent Classification (IPC) or national classification and IPC C07D405/14		
Applicant JANSSEN PHARMACEUTICA N.V.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 4 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 23/10/2000	Date of completion of this report 30.03.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Schmid, A Telephone No. +49 89 2399 8591 

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/04747

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

Description, pages:

1-25 as originally filed

Claims, No.:

1-9 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP00/04747

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-9
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-9
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-9
	No:	Claims	

**2. Citations and explanations
see separate sheet**

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/04747

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- 1) The present compounds differ from the ones of the structurally closest prior art (cf. description, pages 1 and 2) either in the substitution pattern of "A" or simply in the substituent R₅ which makes the present compounds novel pursuant to Article 33(2) PCT.
- 2) The compounds as referred to in the above paragraph are used in various pharmaceutical applications, but nothing is mentioned or suggested with respect to any fundic relaxation properties. Since these unexpected properties could be proved by the applicant (cf. tests on pages 23 -25) together with additional beneficial properties with respect to a vasoconstrictor activity an inventive step in accordance to Article 33(3) PCT can be acknowledged.

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**VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT
AUF DEM GEBIET DES PATENTWESENS**

PCT

INTERNATIONALER RECHERCHENBERICHT

(Artikel 18 sowie Regeln 43 und 44 PCT)

Aktenzeichen des Anmelders oder Anwalts JAB 1488-PCT	WEITERES VORGEHEN siehe Mitteilung über die Übermittlung des internationalen Recherchenberichts (Formblatt PCT/ISA/220) sowie, soweit zutreffend, nachstehender Punkt 5		
Internationales Aktenzeichen PCT/EP 00/04747	<table border="1"> <tr> <td>Internationales Anmeldedatum (Tag/Monat/Jahr) 23/05/2000</td> <td>(Frühestes) Prioritätsdatum (Tag/Monat/Jahr) 02/06/1999</td> </tr> </table>	Internationales Anmeldedatum (Tag/Monat/Jahr) 23/05/2000	(Frühestes) Prioritätsdatum (Tag/Monat/Jahr) 02/06/1999
Internationales Anmeldedatum (Tag/Monat/Jahr) 23/05/2000	(Frühestes) Prioritätsdatum (Tag/Monat/Jahr) 02/06/1999		
Anmelder JANSSEN PHARMACEUTICA N.V.			

Dieser internationale Recherchenbericht wurde von der Internationalen Recherchenbehörde erstellt und wird dem Anmelder gemäß Artikel 18 übermittelt. Eine Kopie wird dem Internationalen Büro übermittelt.

Dieser internationale Recherchenbericht umfaßt insgesamt 3 Blätter.

☒ Darüber hinaus liegt ihm jeweils eine Kopie der in diesem Bericht genannten Unterlagen zum Stand der Technik bei.

1. Grundlage des Berichts

a. Hinsichtlich der **Sprache** ist die internationale Recherche auf der Grundlage der internationalen Anmeldung in der Sprache durchgeführt worden, in der sie eingereicht wurde, sofern unter diesem Punkt nichts anderes angegeben ist.

☐ Die internationale Recherche ist auf der Grundlage einer bei der Behörde eingereichten Übersetzung der internationalen Anmeldung (Regel 23.1 b)) durchgeführt worden.

b. Hinsichtlich der in der internationalen Anmeldung offenbarten **Nucleotid- und/oder Aminosäuresequenz** ist die internationale Recherche auf der Grundlage des Sequenzprotokolls durchgeführt worden, das

☐ in der internationalen Anmeldung in Schriftlicher Form enthalten ist.

☐ zusammen mit der internationalen Anmeldung in computerlesbarer Form eingereicht worden ist.

☐ bei der Behörde nachträglich in schriftlicher Form eingereicht worden ist.

☐ bei der Behörde nachträglich in computerlesbarer Form eingereicht worden ist.

☐ Die Erklärung, daß das nachträglich eingereichte schriftliche Sequenzprotokoll nicht über den Offenbarungsgehalt der internationalen Anmeldung im Anmeldezeitpunkt hinausgeht, wurde vorgelegt.

☐ Die Erklärung, daß die in computerlesbarer Form erfaßten Informationen dem schriftlichen Sequenzprotokoll entsprechen, wurde vorgelegt.

2. ☐ Bestimmte Ansprüche haben sich als nicht recherchierbar erwiesen (siehe Feld I).

3. ☐ Mangelnde Einheitlichkeit der Erfindung (siehe Feld II).

4. Hinsichtlich der Bezeichnung der Erfindung

☒ wird der vom Anmelder eingereichte Wortlaut genehmigt.

☐ wurde der Wortlaut von der Behörde wie folgt festgesetzt:

5. Hinsichtlich der Zusammenfassung

☒ wird der vom Anmelder eingereichte Wortlaut genehmigt.

☐ wurde der Wortlaut nach Regel 38.2b) in der in Feld III angegebenen Fassung von der Behörde festgesetzt. Der Anmelder kann der Behörde innerhalb eines Monats nach dem Datum der Absendung dieses internationalen Recherchenberichts eine Stellungnahme vorlegen.

6. Folgende Abbildung der Zeichnungen ist mit der Zusammenfassung zu veröffentlichen: Abb. Nr. —

☐ wie vom Anmelder vorgeschlagen

☐ keine der Abb.

☐ weil der Anmelder selbst keine Abbildung vorgeschlagen hat.

☐ weil diese Abbildung die Erfindung besser kennzeichnet.

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A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES

IPK 7 C07D405/14 C07D405/12 A61K31/505 A61P9/00

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)

IPK 7 C07D A61K A61P

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

CHEM ABS Data

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
A	WO 97 28157 A (PIERRE FABRE) 7. August 1997 (1997-08-07) in der Anmeldung erwähnt Seite 18 -Seite 25 ---	1-3, 5-9
A	US 5 696 136 A (H.-G. HEINE ET AL.) 9. Dezember 1997 (1997-12-09) Spalte 1 -Spalte 24 ---	1-3, 5-9
A	DE 28 52 945 A (BOEHRINGER) 26. Juni 1980 (1980-06-26) in der Anmeldung erwähnt Seite 1 -Seite 12 ---	1-3, 5-9
A	EP 0 048 218 A (CIBA-GEIGY) 24. März 1982 (1982-03-24) in der Anmeldung erwähnt Ansprüche; Beispiele 1,2 ---	1-3, 5-9

-/--



Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen



Siehe Anhang Patentfamilie

* Besondere Kategorien von angegebenen Veröffentlichungen :

A Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist

E älteres Dokument, das jedoch erst am oder nach dem internationalen Anmeldedatum veröffentlicht worden ist

L Veröffentlichung, die geeignet ist, einen Prioritätsanspruch zweifelhaft erscheinen zu lassen, oder durch die das Veröffentlichungsdatum einer anderen im Recherchenbericht genannten Veröffentlichung belegt werden soll oder die aus einem anderen besonderen Grund angegeben ist (wie ausgeführt)

O Veröffentlichung, die sich auf eine mündliche Offenbarung, eine Benutzung, eine Ausstellung oder andere Maßnahmen bezieht

P Veröffentlichung, die vor dem internationalen Anmeldedatum, aber nach dem beanspruchten Prioritätsdatum veröffentlicht worden ist

T Spätere Veröffentlichung, die nach dem internationalen Anmeldedatum oder dem Prioritätsdatum veröffentlicht worden ist und mit der Anmeldung nicht kollidiert, sondern nur zum Verständnis des der Erfindung zugrundeliegenden Prinzips oder der ihr zugrundeliegenden Theorie angegeben ist

X Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann allein aufgrund dieser Veröffentlichung nicht als neu oder auf erfinderischer Tätigkeit beruhend betrachtet werden

Y Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als auf erfinderischer Tätigkeit beruhend betrachtet werden, wenn die Veröffentlichung mit einer oder mehreren anderen Veröffentlichungen dieser Kategorie in Verbindung gebracht wird und diese Verbindung für einen Fachmann naheliegend ist

G Veröffentlichung, die Mitglied derselben Patentfamilie ist

Datum des Abschlusses der internationalen Recherche

4. Juli 2000

Absendedatum des internationalen Recherchenberichts

13/07/2000

Name und Postanschrift der Internationalen Recherchenbehörde

Europäisches Patentamt, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Bevollmächtigter Bediensteter

Francois, J

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C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
A	EP 0 068 261 A (HOECHST) 5. Januar 1983 (1983-01-05) Ansprüche ---	1-3, 5-9
P, A	WO 99 29687 A (JANSSEN) 17. Juni 1999 (1999-06-17) das ganze Dokument -----	1-9

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/00/04747

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 00/04747

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